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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

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EXAMINER
HUYNH, PHUONG N

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1644	

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20

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,060	Applicant(s) WILLIAMS ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,53-56,59-64 and 66-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49, 53-56, 59-64 and 66-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 49, 53-56, 59-64 and 66-82 are pending.

2. In view of the amendment filed 12/20/02, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 49, 53-56, 59-64 and 66-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein said EtxB (G33D) is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA in vitro, **does not** reasonably provide enablement for (1) a method of treating a subject for *any* allergic or hypersensitivity condition such as asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity comprising administering to the subject an effective amount of *any* agent such as Etx, Ctx, EtxB, and CtxB "mutants or derivatives thereof" that bind to GM1, (2) a method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent that is selected form the group consisting of Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, wherein the agent is administered with any antigen or allergen that is not coupled to any antigen, (3) the said method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent that is selected form the group consisting of Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, wherein the agent is administered with any antigen or allergen that is not coupled to any antigen wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy, (4) a method for treating any subject for an allergic or hypersensitivity condition comprising

administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, (5) the said method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis, and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy, (6) a method for treating a subject for any allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies any GM1-associated activity, wherein the agent is administered with any antigen/allergen, and (7) the said method for treating a subject for any allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies any GM1-associated activity, wherein the agent is administered with any antigen/allergen wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D) for screening for GM1 binding and GM1 associated activity in vitro. The specification discloses only one mutant which is EtxB (G33D) that is a derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant

is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA *in vitro*. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulat or through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20). The specification defines the term "agent" can be one or more of an inorganic or organic chemical, as well as combination thereof, polypeptide, variant/homologue, derivative, fragment thereof so long as they retain the required immunomodulatory activity, it also includes mimics and equivalents and mutants thereof, other agents include antibodies to the target interaction components (page 21).

The specification does not teach how to make and use *any* "mutant" and "derivatives" of any Etx, Ctx, EtxB, CtxB for a method of treating any allergic or hypersensitive conditions mentioned above because "mutant" and "derivative thereof" have no structure, let alone having the same function as wild type Ctx, Etx, CtxB, or EtxB that has certain immunomodulatory activities, in turn, would be effective for treating any allergic disorder. There is insufficient guidance as to which amino acid within the full-length of Ctx, Etx, CtxB, or EtxB can be substitute, delete, or add and whether the resulting mutant, or derivative thereof would maintain the same structure and function such as GM1 associated activity. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality required guidance.

Aman *et al*, of record, teach a mutant of cholera toxin B subunit (CtxB) such as CtxB (H57A) that has a single amino acid substitution from His to Ala lost its immunomodulatory activity although it still binds GM1 ganglioside (See entire document, abstract, in particular). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to binding to GM1, which

modifications would lead to modified GM1-associated activity in vivo, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the indefinite number of "mutant" and "derivative thereof" and the lack of guidance as to which amino acid within the full length of Ext, Ctx, CtxB and EtxB can be modified by substitution, deletion, or addition and still maintain both same structure and function, it is unpredictable which undisclosed Ext, Ctx, CtxB and EtxB "mutant" and "derivative thereof" would bind GM1 and has GM1 associated activity, in turn, would be useful for treating *any* allergic or hypersensitivity condition. Even if the mutant and derivative thereof bind to GM1, binding is not necessary equal to having a specific immune activity, in turn, effective for treating any allergic conditions mentioned above. Further, there are no in vivo working example using *any* Ctx, Etx, CtxB, EtxB, mutants and derivatives thereof for treating *any* allergic or hypersensitivity condition mentioned above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The specification does not describe nor enable any Etx, Ctx, CtxB, or EtxB mutant and derivative of other than EtxB (G33D) for treating any allergic conditions as set forth in claims 49, 53-56, 59-64 and 66-82. Even if the mutant or derivative is limited to EtxB (G33D), there is no showing in the specification as filed that said EtxB (G33D) could treat any allergic disorders mentioned above. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

A method of treatment in the absence of in vivo data are unpredictable for the following reasons: (1) the agent, mutant or derivative thereof may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the agent; (2) the agent, mutant or derivative thereof may not reach the target area because, i.e. the agent may not be able to cross the mucosa or the agent may be adsorbed by fluids, cells and tissues where the agent has no effect; and (3) other functional properties, known or unknown, may make the agent, mutant or derivative thereof unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments in conjunction with the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the publication of Holmgren and Czerkinsky discloses an immunological tolerance inducing agent comprising mucosa-binding agent linked to a specific tolerogen. The PCT WO 95/10301 also includes mentioned of allergy using mucosa binding agent coupled to an allergen. It is implicit within the disclosure of Holmgren and Czerkinsky that the mocosa binding agent must be coupled to the allergen. (2) Tamura et al have taken directly the protocol of WO95/10301 and tested its efficacy in preventing allergy in a murine model of Type I allergy. They reported a significant lowering of IgE levels which are a strong predictor of efficacy but they cite data, following administration of EtxB coupled to ovalbumin, which shows that EtxB was NOT effective once IgE levels are established. While Tamura teach that EtxB-OVA conjugates can prevent allergy, there is no disclosure of suggestion in Tamura et al that EtxB can work in the absence of a conjugated antigen. (3) the experimental result in WO97/02045 would suggest that GM1 binding agent such as EtxB would not find use in the treatment of allergic conditions. (4) There was clear technical prejudice in the art before the priority date of the present invention against using an agent such as EtxB to prevent and/or treat an allergic and/or hypersensitivity condition. (5) Yamamoto et al confirm the generally accepted wisdom in the art at the time the application was filed that agents like Ctx can induce increases in total and specific antigen specific IgE antibodies (page 1206, col. 1 and Table 2) and these are associated with IL4 production (page 1206, col. 2 and Fig 3 and complementary on page 1207, col1). The results of Yamamoto point away from the possible usefulness of agents such as Ctx and mutants thereof in the treatment of allergy because the results in Table 2 indicate that agents such as Ctx and mutants thereof actually promote the production of IgE antibodies which are

known to be the cause of allergy. (6) The data to support the invention in the 37 CFR § 1.132 Declaration accompanying with this amendment demonstrates that, contrary to the generally accepted teachings as set out in the publications such as Yamamoto et al, the EtxB subunit does not promote IgE production but actually suppress the Th2 response. (7) Although Nashar et al teach that IFNγ and IL-2 can be detected in the supernatants from cultures of EtxB and EtxB (G33D) with lymphocyte population, no IL-4, IL-5 and IL-10 could be detected. The teachings of Nashar et al are confined to EtxB subunit and a mutant of the EtxB. In fact, Nashar et al suggest that commercial preparations of Ctx and CtxB or purified CtxB are strongly inhibitory of lymphocyte proliferation. Thus, the conflicting teachings in Nashar et al in relation to Ctx and Etx on lymphocyte proliferation.

In response, Applicant's arguments are not on points with the enablement rejection as set forth in the Office Action mailed 7/16/02. The issues of the enablement rejection are two folds. First, the specification does not teach how to make and use *any* "mutant" and "derivatives" of any Etx, Ctx, EtxB, CtxB for a method of treating any allergic or hypersensitive conditions mentioned above because "mutant" and "derivative thereof" have no structure, let alone having the same function as wild type Ctx, Etx, CtxB, or EtxB that has certain immunomodulatory activities, in turn, would be effective for treating any allergic disorder. There is insufficient guidance as to which amino acid within the full-length of Ctx, Etx, CtxB, or EtxB can be substitute, delete, or add and whether the resulting mutant, or derivative thereof would maintain the same structure and function such as GM1 associated activity. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality required guidance.

Aman *et al*, of record, teach a mutant of cholera toxin B subunit (CtxB) such as CtxB (H57A) that has a single amino acid substitution from His to Ala lost its immunomodulatory activity although it still binds GM1 ganglioside (See entire document, abstract, in particular). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to binding to GM1, which modifications would lead to modified GM1-associated activity in vivo, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338,

footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the indefinite number of "mutant" and "derivative thereof" and the lack of guidance as to which amino acid within the full length of Ext, Ctx, CtxB and EtxB can be modified by substitution, deletion, or addition and still maintain both same structure and function, it is unpredictable which undisclosed Ext, Ctx, CtxB and EtxB "mutant" and "derivative thereof" would bind GM1 and has GM1 associated activity, in turn, would be useful for treating *any* allergic or hypersensitivity condition. Even if the mutant and derivative thereof bind to GM1, binding is not necessary equal to having a specific immune activity, in turn, effective for treating any allergic conditions mentioned above. Further, there are no in vivo working example using *any* Ctx, Etx, CtxB, EtxB, mutants and derivatives thereof for treating *any* allergic or hypersensitivity condition mentioned above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Second, the specification does not enable any Etx, Ctx, CtxB, or EtxB mutant and derivative of other than EtxB (G33D) for treating any allergic conditions at the time of filing. Even if the mutant or derivative is limited to EtxB (G33D), there is no showing in the specification as filed that said EtxB (G33D) could treat any allergic disorders mentioned above. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). A method of treatment in the absence of in vivo data are unpredictable for the following reasons: (1) the agent, mutant or derivative thereof may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the agent; (2) the agent, mutant or derivative thereof may not reach the target area because, i.e. the agent may not be able to cross the mucosa or the agent may be adsorbed by fluids, cells and tissues where the agent has no effect; and (3) other functional properties, known or unknown, may make the agent, mutant or derivative thereof unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In response to the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams, the data provided in the Katz declaration is limited to treating asthma using EtxB. The data does not show any mutant and derivative of any EtxB, Etx, Ctx and CtxB that are effective for treating any

allergic conditions. While applicant has provided in vivo data as evidence of enablement for EtxB for treating Asthma, the data provides little assistance in enabling the PTO to determine applicant's assertions of conception, diligence and reduction to practice at the time of filing.

5. Claims 49, 53-56, 59-64 and 66-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of treating a subject for *any* allergic or hypersensitivity condition such as asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity comprising administering to the subject an effective amount of *any* agent such as Etx, Ctx, EtxB, and CtxB "mutants or derivatives thereof" that bind to GM1, (2) a method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent that is selected form the group consisting of Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, wherein the agent is administered with any antigen or allergen that is not coupled to any antigen, (3) the said method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent that is selected form the group consisting of Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, wherein the agent is administered with any antigen or allergen that is not coupled to any antigen wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy, (4) a method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity, (5) the said method for treating any subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies a GM1-associated activity wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis, and conjunctivitis,

atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy, (6) a method for treating a subject for any allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies any GM1-associated activity, wherein the agent is administered with any antigen/allergen, and (7) the said method for treating a subject for any allergic or hypersensitivity condition comprising administering to the subject an effective amount of any agent such as Ctx, Etx, CtxB, EtxB or *any* "mutant or derivative thereof" that modifies any GM1-associated activity, wherein the agent is administered with any antigen/allergen wherein the allergic condition is selected from the group consisting of asthma, allergic cough, allergic rhinitis,and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, or contact hypersensitivity such as plant poison ivy.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D) for screening for GM1 binding and GM1 associated activity in vitro. The specification discloses only one mutant which is EtxB (G33D) that is a derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA *in vitro*. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulat or through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20). The specification defines the term "agent" can be one or more of an inorganic or organic chemical, as well as combination thereof, polypeptide, variant/homologue, derivative, fragment thereof so long as they retain the required immunomodulatory activity, it also includes mimics and equivalents and mutants thereof, other agents include antibodies to the target interaction components (page 21).

With the exception of the specific Etx, Ctx, EtxB, CtxB, and EtxB (G33D) mentioned above for in vitro screening assays, there is insufficient written description about the structure

associated with function of (1) *any* "mutants" or "derivatives" of Etx, Ctx, CtxB, or EtxB because the term "mutants" or "derivatives" have no structure, much less function. Let alone capable of treating any allergic conditions. Further, the specification discloses only one mutant, that is EtxB (G33D) derived from EtxB. Even if the mutant and derivative is limited to EtxB (G33D), there is inadequate written description about the method of treating any allergic conditions.

Given the lack of a written description of *any* additional representative species of "mutant" and "derivative thereof", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments in conjunction with the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the publication of Holmgren and Czerkinsky discloses an immunological tolerance inducing agent comprising mucosa-binding agent linked to a specific tolerogen. The PCT WO 95/10301 also includes mentioned of allergy using mucosa binding agent coupled to an allergen. It is implicit within the disclosure of Holmgren and Czerkinsky that the mocosa binding agent must be coupled to the allergen. (2) Tamura et al have taken directly the protocol of WO95/10301 and tested its efficacy in preventing allergy in a murine model of Type I allergy. They reported a significant lowering of IgE levels, which are a strong predictor of efficacy, but they cite data, following administration of EtxB coupled to ovalbumin, which shows that EtxB was NOT effective once IgE levels are established. While Tamura teach that EtxB-OVA conjugates can prevent allergy, there is no disclosure of suggestion in Tamura et al that EtxB can work in the absence of a conjugated antigen. (3) the experimental result in WO97/02045 would suggest that GM1 binding agent such as EtxB would not find use in the treatment of allergic conditions. (4) There was clear technical prejudice in the art before the priority date of the present invention against using an agent such as EtxB to prevent and/or treat an allergic and/or hypersensitivity condition. (5) Yamamoto et al confirm the generally accepted wisdom in the art at the time the application was filed that agents like Ctx can induce increases in total and specific antigen specific IgE antibodies (page 1206, col. 1 and Table 2) and these are

associated with IL4 production (page 1206, col. 2 and Fig 3 and complementary on page 1207, col1). The results of Yamamoto point away from the possible usefulness of agents such as Ctx and mutants thereof in the treatment of allergy because the results in Table 2 indicate that agents such as Ctx and mutants thereof actually promote the production of IgE antibodies, which are known to be the cause of allergy. (6) The data to support the invention in the 37 CFR § 1.132 Declaration accompanying with this amendment demonstrates that, contrary to the generally accepted teachings as set out in the publications such as Yamamoto et al, the EtxB subunit does not promote IgE production but actually suppress the Th2 response. (7) Although Nashar et al teach that IFNγ and IL-2 can be detected in the supernatants from cultures of EtxB and EtxB (G33D) with lymphocyte population, no IL-4, IL-5 and IL-10 could be detected. The teachings of Nashar et al are confined to EtxB subunit and a mutant of the EtxB. In fact, Nashar et al suggest that commercial preparations of Ctx and CtxB or purified CtxB are strongly inhibitory of lymphocyte proliferation. Thus, the conflicting teachings in Nashar et al in relation to Ctx and Etx on lymphocyte proliferation.

In response, Applicant's arguments are not on points with the enablement rejection as set forth in the Office Action mailed 7/16/02. The issues of a written description are: there is insufficient written description about the structure associated with function of (1) *any* "mutants" and (2) "derivatives" of Etx, Ctx, CtxB, or EtxB because the term "mutants" or "derivatives" have no structure, much less function. Let alone capable of treating any allergic conditions. Further, the specification discloses only one mutant, that is EtxB (G33D) derived from EtxB. Even if the mutant and derivative is limited to EtxB (G33D), there is inadequate written description about the method of treating any allergic conditions using any Etx, Ctx, CtxB, or EtxB. Given the lack of a written description of *any* additional representative species of "mutant" and "derivative thereof", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (of record, April 1995, PTO 1449) in view of WO 97/02045 publication (of record, Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449).

The WO 95/10301 publication teaches a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions to human gamma globulins comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or the B subunit of cholera toxin (CTB) conjugated to an antigen such as ragweed pollen (page 14, line 16), or human gamma globulins or Red blood cell (RBC) (See pages 23, 24, Example 1, pages 26 and 32, Tables 2-9, claims 16, 1-5, 8, 9, in particular). The reference LTB and CTB bind to GM1 (See page 17, lines 23-30, in particular) and have an effect on GM1 mediated intracellular signaling events such as prolonged graft survival, suppression of EAE (See pages 28-29, in particular). The reference LTB and CTB are the same as the claimed EtxB and CtxB, respectively. The WO 95/10301 publication teaches mucosally induced systemic tolerance can be utilized to reduce or suppress immune responses not only against foreign an

The claimed invention as recited in claim 49 differs from the teachings of reference only that the agent is not coupled to an antigen.

The claimed invention as recited in claim 51 differs from the teachings of reference only that the agent has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the agent is selected from the group consisting of Etx, Ctx, CtxB, EtxB and mutants or derivatives thereof that bind to GM1.

The claimed invention as recited in claim 56 differs from the teachings of reference only that the agent modifies a GM1-assciated activity wherein the agent is not coupled to an antigen.

The claimed invention as recited in claim 61 differs from the teachings of reference only that the agent is selected from the group consisting of CtxB, EtxB or a mutant or derivatives thereof that modifies a GM1-associated activity and is not coupled to an antigen.

The WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (not coupled) (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular).

Nashar *et al* teach agent such as E. Coli heat-labile enterotoxin (Etx) which is closely related homologue cholera toxin (Ctx) EtxB and mutant such as EtxB (G33D) and their respective B subunits are potent mucosal and systemic immunogens and potential carriers (See page 226, column 1, in particular). The reference B subunits Etx and Ctx bind to GM1 and modulate immune response such as serum antibody response (See page 228, Fig 2, in particular). Nashar *et al* further teach mutant or derivative of Etx such as EtxB (G33D), which is a mutant having a Gly to Asp substitution at residue 33; the reference EtxB (G33D) fails to bind to GM1 but has an effect on GM1 mediated intracellular signaling events such as lymphocyte proliferation (Table 1, in particular). Nashar *et al* teach the reference ExtB stimulates B and T cells activation (See Fig 4, in particular) while EtxB (G33D) mutant decreases B and T cell activation, but increases IFNγ production (See Table 2, in particular). Further, the reference teaches EtxB but not EtxB (G33D) causes complete depletion of CD8+ cells by apoptosis (See page 230, column 1, second full paragraph, in particular). Nashar *et al* teach that the potent immunogenicity of the reference

agents is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to substitute the agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication for the derivative or mutant such as EtxB (G33D) or agent such as EtxB as taught by the WO 97/02045 publication or the Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 97/02045 publication teaches the reference agent is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Applicants' arguments in conjunction with the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the publication of Holmgren and Czerkinsky (WO 95/10301) discloses an immunological tolerance inducing agent comprising mucosa-binding agent linked to a specific tolerogen. The PCT WO 95/10301 also includes mentioned of allergy using mucosa binding agent coupled to an allergen. It is implicit within the disclosure of Holmgren and Czerkinsky that the mocosa binding agent must be coupled to the allergen. (2) Tamura et al have taken directly the protocol of WO95/10301 and tested its efficacy in preventing allergy in a murine model of Type I allergy. They reported a significant lowering of IgE levels, which are a strong predictor of efficacy, but they cite data, following administration of EtxB coupled to ovalbumin, which shows that EtxB was NOT effective once IgE levels are established. While Tamura teach that EtxB-OVA conjugates can prevent allergy, there is no disclosure of suggestion in Tamura et al that EtxB can work in the absence of a conjugated antigen. (3) the experimental result in WO97/02045 would suggest that GM1 binding agent such as EtxB would not find use in the treatment of allergic conditions. (4) There was clear technical prejudice in the art before the priority date of the present invention against using an agent such as EtxB to prevent

and/or treat an allergic and/or hypersensitivity condition. (5) Yamamoto et al confirm the generally accepted wisdom in the art at the time the application was filed that agents like Ctx can induce increases in total and specific antigen specific IgE antibodies (page 1206, col. 1 and Table 2) and these are associated with IL4 production (page 1206, col. 2 and Fig 3 and complementary on page 1207, col1). The results of Yamamoto point away from the possible usefulness of agents such as Ctx and mutants thereof in the treatment of allergy because the results in Table 2 indicate that agents such as Ctx and mutants thereof actually promote the production of IgE antibodies, which are known to be the cause of allergy. (6) The data to support the invention in the 37 CFR § 1.132 Declaration accompanying with this amendment demonstrates that, contrary to the generally accepted teachings as set out in the publications such as Yamamoto et al, the EtxB subunit does not promote IgE production but actually suppress the Th2 response. (7) Although Nashar et al teach that IFNγ and IL-2 can be detected in the supernatants from cultures with EtxB and EtxB (G33D) with lymphocyte population, no IL-4, IL-5 and IL-10 could be detected. The teachings of Nashar et al are confined to EtxB subunit and a mutant of the EtxB. In fact, Nashar et al suggest that commercial preparations of Ctx and CtxB or purified CtxB are strongly inhibitory of lymphocyte proliferation. Thus, the conflicting teachings in Nashar et al in relation to Ctx and Etx on lymphocyte proliferation.

In response to Applicant's arguments that the publication of Holmgren and Czerkinsky (WO 95/10301) implicitly teaches that the mocosa binding agent must be coupled to the allergen, the claimed method comprising unconjugated allergen is an obvious variation of the reference teachings because the starting materials of the reference Ctx-conjugated allergen are unconjugated to begin with.

In contrast to Applicant's assertion that there is no disclosure of suggestion in Tamura et al that EtxB can work in the absence of a conjugated antigen, Tamura et al that EtxB-OVA conjugates can prevent allergy (See Table 1, page 227, in particular). Tamura et al further teach that intranasal administering LTB-OVA together with free LT or LTB-OVA, or a mixture of **OVA and LTB (unconjugated)** three days before systemic immunization. The results shown in Fig 2 indicate that the mixture of OVA and LTB treated group still inhibit DTH while the free LT abrogated the suppression of both DTH and IgE responses.

In contrast to Applicant's assertion that the experimental result in WO97/02045 would suggest that GM1 binding agent such as EtxB would not find use in the treatment of allergic conditions, the WO 97/02045 publication teaches a method for treating a subject comprising

administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (not coupled) (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant because it induce apoptosis in CD8+ T cell population (See claim 16 of WO 97/02045, in particular) as well as increase IFNγ and IL-2 production which can be detected in the supernatants from EtxB or EtxB (G33D) cocultured with lymphocyte (See Table 2 on page 41, page 31, lines 12-13, in particular). Both IFNγ and IL-2 are classical Th1 cytokine which are known to cross-regulate Th2 immune response.

In contrast to Applicant's assertion that there was clear technical prejudice in the art before the priority date of the present invention against using an agent such as EtxB to prevent and/or treat an allergic and/or hypersensitivity condition, Tamura et al, of record, clearly show that the key difference between LT (holotoxin) or LTB lies within the B subunit since free LT coadministering with LTB-OVA abrogated the suppression of both DTH and IgE responses (Fig 2, page 228, in particular). Tamura et al further teach that oral or nasal tolerance to some antigen is abrogated by the oral or nasal administration of antigen coupled to or together with cholera toxin/cholera toxin B subunit (CT/CTB) containing trace amount of CT (See page 225, column 1, in particular).

In response to Applicant's argument that citing Yamamoto et al as a reference confirming the generally accepted wisdom in the art at the time the application was filed that agents like Ctx can induce increases in total and specific antigen specific IgE antibodies (page 1206, col. 1 and Table 2), it is noted that the Yamamoto reference is not cited in this rejection.

Yamamoto *et al.* teach an assay method for identifying agent such as mutant or derivative of cholera toxin (S61F and E112K) and heat labile toxin (LT) of E coli by measuring (1) a change in the antigen (Ova) specific IgE (See page 1204, right column, IgE analysis, in particular) (2) a change in the production of Th2 associated cytokines such as IL-4, IL-10 by ELISA (See page 1205, left column, Fig 3, in particular), (3) the effect of the agent on the GM1 mediated intracellular signaling events such as ADP-ribosyltransferase (See page 1204, right column, in particular), (4) measuring antigen specific T-cell reactivity such as T cell proliferation (See page 1207, Fig 2, page 1204, right column OVA- and CT-B specific CD4 T cell responses, in particular), (5) a change in antigen specific IgG levels (See page 1206, Fig 1, in particular). Yamamoto *et al* teach that antigen specific **IgE level for mutant S61F is reduced** (See page

1206, left column). Yamamoto *et al* further teach that the adjuvanicity of cholera toxin can be dissociated from the GM1 mediated intracellular signaling events such as ADP-ribosyltransferase activity and enterotoxicity using site directed mutagenesis to create mutant or derivative and measure various immune responses mentioned above (see page 1207, right column, in particular).

In response to the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams, the data provided in the Katz declaration is limited to treating asthma using EtxB. The data does not show any mutant and derivative of any EtxB, Etx, Ctx and CtxB which are effective for treating any allergic conditions. While applicant has provided in vivo data as evidence of enablement for EtxB for treating Asthma, the data provides little assistance in enabling the PTO to determine applicant's assertions of conception, diligence and reduction to practice at the time of filing.

In response to Applicant's argument that Nashar et al teach that IFNγ and IL-2 can be detected in the supernatants from cultures with EtxB and EtxB (G33D) with lymphocyte population, no IL-4, IL-5 and IL-10 could be detected, the results pointed out by Applicant further affirm the use of ExtB and EtxB (G33D) for a method of treating allergic condition because both IFNγ and IL-2 are Th1 cytokines which cross-regulates Th2 immune response. Further, the lack of detection for IL-4 which is a key regulator of IgE synthesis would indicate that it is good for allergic condition since allergy is associated with increase IL-4, in turn, it leads to the increase in the production of IgE.

In response to Applicant's argument that commercial preparations of Ctx and CtxB or purified CtxB are strongly inhibitory of lymphocyte proliferation, Nashar et al further teach that the potent immunogenicity of Ctx and Etx and their subunits is well documented. However, their precise way in which they stimulate strong immune response depends on lymphocytes populations, activation status of the lymphocytes population as well as the inherent properties of these Etx and CtxB proteins (See Discussion, in particular).

9. Claims 54, 60, 61, 64, 66-69, 70, 72, 73, 74, 75, 77, 78, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (of record, April 1995, PTO 1449) in view of WO 97/02045 publication (Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449) as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 mentioned above and further in view of Roitt *et al* (of record, in Immunology, 2nd edition, pages 19.1-19.3, 1989, PTO 892) and Patterson *et al* (of record, J immunol 117(1): 97-101, July 1976, PTO 892).

The teachings of the WO 95/10301 publication, the WO 97/02045 publication and Nashar *et al* have been discussed supra.

The claimed invention as recited in claims 54, 60, 64, 66 and 81 differs from the teachings of the references only by the recitation that the treatment is for asthma.

The claimed invention as recited in claims 67, 74 and 78 differs from the teachings of the references only by the recitation that the hypersensitivity condition is contact sensitivity.

The claimed invention as recited in claims 66, 69 73 and 77 differs from the teachings of the references only by the recitation that the allergic condition is asthma, allergic rhinitis, atopic eczema, uticaria, insect bite allergy.

The claimed invention as recited in claims 68, 72, 75 and 82 differs from the teachings of the references only by the recitation that the treatment is for allergic rhinitis.

The claimed invention as recited in claim 70 differs from the teachings of the references only by that the method wherein the hypersensitivity condition is contact sensitivity induced by plant poison ivy.

Roitt *et al* teach hypersensitivity (type I) such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom is characterized by an allergic reaction immediately following contact (contact hypersensitivity) with an allergen (See page 19.2, in particular). Roitt *et al* teach IgE levels are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular) and the production of IgE is controlled by IL-4, which is a Th2 cytokine (See page 19.5, column 1, in particular). Roitt *et al* further teach the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular).

Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to include asthma as one of the hypersensitivity condition as taught by Roitt *et al* using the agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication or the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the agent such as Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Roitt *et al* teach the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular). Claim 70 is included in this rejection since it is within the purview of one skill in the art at the time the invention was made because Roitt *et al* teach hypersensitivity (type I) such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom is characterized by an allergic reaction immediately following contact (contact hypersensitivity) with an allergen (See page 19.2, in particular) and the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular).

Applicants' arguments filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 50 and 58 related to effects of IgE-mediated response are moot by the amendment to the claims which eliminate all references to IgE.

However, claims 54, 60, and 64-65 recite that the treatment is for asthma.

Roitt *et al* teach asthma is a hypersensitivity (type I) which occurs when an IgE response is directed against innocuous antigen such as pollen, the resulting release of pharmacological mediators such as histamine by IgE sensitized mast cells produces an acute inflammatory reaction with symptoms such as asthma and the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular).

10. Claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable Tamura *et al* (of record, Vaccine 15(2): 225-229, 1997, PTO 892) in view of WO 97/02045 publication (of record, Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449).

Tamura *et al* teach a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or LT coupled or conjugated to an antigen such as ovalbumin (See abstract, page 227, column 1, in particular). The reference LTB and CTB bind to GM1 (See page 226, Preparation of LTB-LT conjugated antigen, in particular). The reference LT and LTB are the same as the claimed Etx and EtxB, respectively. The reference ovalbumin (OVA) coupled to LTB suppresses

the induction of both DTH and IgE antibody responses (See page 225, column 2,Table 1, in particular). Tamura *et al* teach LTB-coupled OVA is useful for suppressing the induction of both DHT and IgE antibody responses and LTB as well as CTB can serve as a powerful carrier induction of immunologial tolerance (See page 228, column 1, first full paragraph, in particular).

The claimed invention as recited in claim 49 differs from the teachings of the reference only by that the agent is not coupled to an antigen.

The claimed invention as recited in claim 51 differs from the teachings of the reference only that the agent has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity.

The claimed invention as recited in claim 52 differs from the teachings of the reference only that the agent is selected from the group consisting of Etx, Ctx, CtxB, EtxB and mutants or derivatives thereof that bind to GM1.

The claimed invention as recited in claim 56 differs from the teachings of the reference only that the agent modifies a GM1-assciated activity and wherein the agent is not coupled to an antigen.

The claimed invention as recited in claim 61 differs from the teachings of the reference only that the agent is selected from the group consisting of CtxB, EtxB or a mutant or derivatives thereof that modifies a GM1-associated activity and is not coupled to an antigen.

The WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular).

Nashar *et al* teach agent such as E. Coli heat-labile enterotoxin (Etx) which is closely related homologue cholera toxin (Ctx) EtxB and mutant such as EtxB (G33D) and their respective B subunits are potent mucosal and systemic immunogens and potential carriers (See page 226, column 1, in particular). The reference B subunits Etx and Ctx bind to GM1 and modulate immune response such as serum antibody response (See page 228, Fig 2, in particular). Nashar *et al* further teach mutant or derivative of Etx such as EtxB (G33D), which is a mutant having a Gly to Asp substitution at residue 33; the reference EtxB (G33D) fails to bind to GM1 but has an effect on GM1 mediated intracellular signaling events such as lymphocyte proliferation (Table 1,

in particular). Nashar *et al* teach the reference ExtB stimulates B and T cells activation (See Fig 4, in particular) while EtxB (G33D) mutant decreases B and T cell activation, but increases IFNγ production (See Table 2, in particular). Further, the reference teaches EtxB but not EtxB (G33D) causes complete depletion of CD8+ cells by apoptosis (See page 230, column 1, second full paragraph, in particular). Nashar *et al* teach that the potent immunogenicity of the reference agents is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to use unconjugated agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the unconjugated Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the Tamura *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Tamura *et al* teach LTB as well as CTB can serve as a powerful carrier induction of immunologial tolerance such as DHT and IgE responses (See page 228, column 1, first full paragraph, in particular). The WO 97/02045 publication teaches the reference agent is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Applicants' arguments filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that this rejection is premised on a hindsight view for there is no suggestion in the references that Applicant's invention would be efficacious in the treatment of asthma as illustrated in the Declaration.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In response to the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams, the data provided in the Katz declaration is limited to treating asthma using EtxB. The data does not show any mutant and derivative of any EtxB, Etx, Ctx and CtxB which are effective for treating any allergic conditions. While applicant has provided in vivo data as evidence of enablement for EtxB for treating Asthma, the data provides little assistance in enabling the PTO to determine applicant's assertions of conception, diligence and reduction to practice at the time of filing. The specification as filed provides no working in vivo example demonstrating any EtxB, Etx, Ctx and CtxB, mutants and derivatives thereof are efficacious in the treatment of any allergic condition or hypersensitivity reactions such as asthma.

11. Claims 54, 60, 61, 64, 66-69, 70 72, 73, 74, 75, 77, 78 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable Tamura *et al* (of record, Vaccine 15(2): 225-229, 1997, PTO 892) in view of WO 97/02045 publication (of record, Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449) as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 mentioned above, and further in view of Roitt *et al* (of record, in Immunology, 2nd edition, pages 19.1-19.3, 1989, PTO 892).

The teachings of Tamura *et al*, the WO 97/02045 publication and Nashar *et al* have been discussed supra.

The claimed invention as recited in claims 54, 60, 64, 66 and 81 differs from the teachings of the references only that the treatment is for asthma.

The claimed invention as recited in claims 67, 74 and 78 differs from the teachings of the references only by the recitation that the hypersensitivity condition is contact sensitivity.

The claimed invention as recited in claims 66, 69 73 and 77 differs from the teachings of the references only that the allergic condition is asthma, allergic rhinitis, atopic eczema, uticaria, insect bite allergy.

The claimed invention as recited in claims 68, 72, 75 and 82 differs from the teachings of the references only that the treatment is for allergic rhinitis.

The claimed invention as recited in claim 70 differs from the teachings of the references only that the hypersensitivity condition is contract sensitivity by plant poison ivy.

Roitt *et al* teach hypersensitivity (type I) such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom is characterized by an allergic reaction immediately following contact (contact hypersensitivity) with an allergen (See page 19.2, in particular). Roitt *et al* teach IgE levels are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular) and the production of IgE is controlled by IL-4, which is a Th2 cytokine (See page 19.5, column 1, in particular). Roitt *et al* further teach the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to treat asthma or allergic rhinitis as one of the hypersensitivity conditions as taught by Roitt *et al* using the agent such as LTB (EtxB) or LT (Etx) as taught by Tamura *et al* or the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the agent such as Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Roitt *et al* teach the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom (See page 19.5, column 1, page 19.2, in particular). Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular). Tamura *et al* teach LTB as well as CTB can serve as a powerful carrier induction of immunologial tolerance such as DHT and IgE responses (See page 228, column 1, first full paragraph, in particular). Claim 70 is included in this rejection because contact hypersensitivity such as plant poison ivy is within the purview of one skill in the art at the time the invention was made because Roitt *et al* the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom as well as contact sensitivity (See page 19.5, column 1, page 19.2, in particular).

Applicants' arguments filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that this rejection is premised on a hindsight view for there is no suggestion in the references that Applicant's invention would be efficacious in the treatment of asthma as illustrated in the Declaration. The claims rejections for asthma treatments. The references are not directed to asthma. There is no suggestion in the references that the agents Applicants claim would be effective in the treatment of asthma.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971).

In response to the declaration under 37 C.F.R. 1.132 by Neil Andrew Williams, the data provided in the Katz declaration is limited to treating asthma using EtxB. The data does not show any mutant and derivative of any EtxB, Etx, Ctx and CtxB which are effective for treating any allergic conditions. While applicant has provided in vivo data as evidence of enablement for EtxB for treating Asthma, the data provides little assistance in enabling the PTO to determine applicant's assertions of conception, diligence and reduction to practice at the time of filing. The specification as filed provides no working in vivo example demonstrating any EtxB, Etx, Ctx and CtxB, mutants and derivatives thereof are efficacious in the treatment of any allergic condition or hypersensitivity reactions such as asthma.

In response to applicant's argument that the references are not directed to asthma treatment, Roitt *et al* teach asthma is related to hypersensitivity (type I) which occurs when an IgE response is directed against innocuous antigen such as pollen, the resulting release of pharmacological mediators such as histamine by IgE sensitized mast cells produces an acute inflammatory reaction with symptoms such as asthma and the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular). Tamura et al that EtxB-OVA conjugates can prevent allergy (See Table 1, page 227, in particular). Tamura et al further teach that intranasal administering LTB-OVA together with free LT or LTB-OVA, or a mixture of **OVA and LTB** three days before systemic immunization. The results shown in Fig 2 indicate that the mixture of OVA and LTB treated group still inhibit DTH while the free LT abrogated the suppression of both DTH and IgE responses. In response to applicant's argument that there is no

suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the goal of treatment is to redirect the immune response to a Th1 response from a Th2 immune response using Ctx, Etx, CtxB, EtxB as taught by the Tamura *et al*, the WO 97/02045 publication and Nashar *et al*.

12. The following new ground of objection is necessitated by the amendment filed 12/20/02.

13. Claim 72 is objected to because of typographical error "tretment".

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
Technology Center 1600
March 10, 2003

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